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10/621,958	07/16/2003	Steven J. Locke	357000-1200	2039

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EXAMINER	
VENCI, DAVID J	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,958	LOCKE ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 9, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-14,17-23,28 and 32-36* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-14,17-23 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-14,17-23,28 and 32-36* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *July 16, 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/09/07*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20070301* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply, filed March 9, 2007, which cancelled claims 15 and 16. Claim 28 is drawn to a non-elected invention and remains withdrawn from consideration. Currently, claims 4-14, 17-23 and 32-36 are under examination.

Specification

The disclosure is objected to because of the following informalities:

In paragraph [00126]:

In sentence 2, the phrase "each sample" is vague. Whether "each sample" references any object recited in sentence 1 of paragraph [00126] OR/XOR labeled, reduced product of sentence 1 of paragraph [00126].

In sentence 3, the phrase "the molecules" lacks basis in prior sentences.

In sentence 4, the abbreviation "API III+" is vague because the identity of one or more objects referenced by the abbreviation "API III+" is not clear.

In sentence 4, the proper noun "IonSpray" is vague. The identity of one or more "IonSpray" sources, if any, is not clear.

In sentence 6, the phrase "the amines" lacks basis in prior sentences and/or is vague. Whether "the amines" references any object recited in sentence 1 of paragraph [00126] OR/XOR labeled, reduced product of sentence 1 of paragraph [00126].

In paragraph [00127]: (*i.e.*, Table 2)

The phrase "various amines" is vague. Whether the phrase references compounds listed in Table 2 in column labeled "Compound" AND/OR/XOR any object recited in sentence 1 of paragraph [00126] AND/OR/XOR labeled, reduced product of sentence 1 of paragraph [00126] AND/OR/XOR "the amines" referenced in sentence 6 of paragraph [00126] is not clear.

Table 2 fails to indicate whether Applicants used cyanoborohydride or cyanoborodeuteride, or how Applicants weighed the stuff in columns 3 and 4.

Appropriate correction is required.

Drawings

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to under 37 CFR 1.83(a). Specifically, the lower panel of Fig. 8 fails to show "3-aminothiophenol labelled with CH_2O (m/z = 123.0) and CD_2O (m/z = 127.0) and $NaCNBH_3$" as described in the specification paragraph [00126], sentence 12 (need more mass). The identity of compounds detected in the lower panel of Fig. 8 is not clear because the expected mass for a methyl- or dimethyl- derivative of 3-aminothiophenol should be at least 139.193 and 153.193, respectively.

Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d).

In addition, the compounds in the upper panel of Fig. 8 appear too dark.

Claim Rejections - 35 USC § 112 – first paragraph
New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-14, 17-23 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter not described in the specification in such a way so as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, independent claims 32, 33 and 36, as amended, are directed to methods comprising, *inter alia*, labeling reagents containing aldehyde AND reducing agent. Examiner is unable to locate support in Applicants' original specification for labeling reagents containing aldehyde AND reducing agent. Examiner is unable to locate support in Applicants' original specification for methods incorporating labeling reagents containing aldehyde AND reducing agent. According to para. [0095]:

> "an aldehyde is combined with the buffer and then mixed with the sample in the presence of the reducing agent"

Applicants' description of "sample in the presence of the reducing agent" is not equivalent to the claimed aldehyde AND reducing agent required in step (i) of claims 32, 33 and 36.

Applicants are required to cancel new matter.

Claim Rejections - 35 USC § 112 – first paragraph
Lack of Enablement

Claims 4-14, 17-23 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter not described in the specification in a way to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, independent claims 32, 33 and 36, as amended, are directed to "quantitative" methods comprising, *inter alia*, a step of "reacting" reagents containing aldehyde AND reducing agent.

Applicants' specification does not describe methods using labeling reagents containing aldehyde AND reducing agent[1], much less "quantitative" methods using the same.

According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

[1] At best, Applicants' specification describes methods wherein "an aldehyde is combined with the buffer and then mixed with the sample in the presence of the reducing agent" (see para. [0095] and Examples 1-6, 9 and 10).

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the amount of direction in Applicants' specification, by way of working examples or otherwise, is limited because Applicants' specification does not disclose reference standards, instrument-specific data treatment algorithms or an instrument.[2,3,4]

In addition, the state of the prior art indicates a high level of unpredictability in "quantitative" mass spectrometry:

1. According to Carr & Annan, CURRENT PROTOCOLS IN PROTEIN SCIENCE, Unit 16.1, pp. 16.1.1-16.1.27, John Wiley & Sons, Inc. (1996), internal reference standards are required for "quantitative" mass spectrometry because data interpretation is affected by such factors as differing ionization efficiencies (see p. 16.1.15, right column, *Is MS data quantitative*), instrument-specific mass resolution (see paragraph bridging pp. 16.1.19 – 16.1.20), instrument-specific data treatment algorithms (see p. 16.1.21, paragraph bridging left and right columns) and adduct formation (see paragraph bridging pp. 16.1.21 – 16.1.22).

2. According to Robbins (US 5,939,229), mass spectrometer data interpretation is also affected by various isotope exchange reactions, thereby necessitating "predetermined"[5] reference standards (see Abstract).

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[2] In the Specification paragraph [00126], Applicants disclose "API III+ with an IonSpray source" instrument, which Examiner raises objection, *supra*, Section entitled *Specification*, because the abbreviation "API III+" is vague (the identity of one or more objects referenced by the abbreviation "API III+" is not clear).

[3] Examiner reiterates objection to the lower panel of Fig. 8 for not showing "3-aminothiophenol labelled with CH_2O (m/z = 123.0) and CD_2O (m/z = 127.0) and $NaCNBH_3$" as described in the specification paragraph [00126], sentence 12 (the expected mass for a methyl- or dimethyl- derivative of 3-aminothiophenol should be at least 139.193 and 153.193, respectively).

[4] Examiner reiterates objection to Table 2 of Example 7 for not indicating whether Applicants used cyanoborohydride or cyanoborodeuteride, or how Applicants weighed the stuff in columns 3 and 4.

3. Finally, Arend *et al.*, 37 ANGEW. CHEM. INT. ED. 1044 (1998), teach aldehyde-reductant labeling reagents might produce side-reactions with enol tautomers of carbonyl compounds (see Scheme 1) which might be present in complex analyte samples.

Given the aforementioned deficiencies, Examiner posits that undue experimentation is required to remake and use Applicants' invention, as claimed.

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[5] See also, Croarkin & Tobias, NIST/SEMATECH e-Handbook of Statistical Methods, *available at* <http://www.itl.nist.gov/div898/handbook/>, (noting "[t]he most critical element of any measurement process is the relationship between a single measurement and the reference base for the unit of measurement").

Claim Rejections - 35 USC § 112 – second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-14, 17-23 and 32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 32, 33 and 36:

In step (i), the phrase "an aldehyde selected from formaldehyde and acetaldehyde and a reducing agent" is indefinite. Whether Applicants intend a Markush-type claim is not clear. The identity of two or more Markush members is not clear.

In step (i), the phrase "each of the up to 8 combinations of differential isotope labeled reagents is isotopically distinct" is indefinite, wherein "providing up to 8 combinations" = 1. Whether/how 1 acetaldehyde-reducing agent reagent is "differential isotope labeled" is not clear. Whether/how 1 acetaldehyde-reducing agent reagent is "isotopically distinct" is not clear. The identity of one or more reference objects required for ascertaining "isotopically distinct" is not clear, wherein "providing up to 8 combinations" = 1.

In claim 32:

In step (ii), the phrase "reacting each of the up to 8 samples comprising molecules with one of the up to 8 combinations of differential isotope labeled reagents" is indefinite, wherein "providing up to 8 combinations" = 2 to 8. The purpose of acetaldehyde-reducing agent reagent classes 2 through 8 in the overall method is not clear and appears omitted from the claim.

In step (ii), the phrase "to produce up to 8 samples of differential isotope labeled derivatives of molecules" is indefinite, wherein "providing up to 8 combinations" = 1. The identity of one or more reference objects required for ascertaining "differential isotope labeled" is not clear, wherein "providing up to 8 combinations" = 1.

In claim 33:

In step (ii), the phrase "reacting each of the samples comprising molecules with one of the up to 8 combinations of reagents" is indefinite, wherein "providing up to 8 combinations" = 2 to 8. The purpose of acetaldehyde-reducing agent reagent classes 2 through 8 in the overall method is not clear and appears omitted from the claim.

In step (ii), the phrase "to provide up to 8 samples of differential isotope labeled derivatives of molecules" is indefinite, wherein "providing up to 8 combinations" = 1. The identity of one or more reference objects required for ascertaining "differential isotope labeled" is not clear, wherein "providing up to 8 combinations" = 1.

In claim 36:

In step (ii), the phrase "reacting each sample with one of the combinations of differential isotope labeled reagents" is indefinite, wherein "providing up to 8 combinations" = 2 to 8. The purpose of acetaldehyde-reducing agent reagent classes 2 through 8 in the overall method is not clear and appears omitted from the claim.

In step (ii), the phrase "to produce up to 8 samples of differential isotope labeled derivatives of molecules" is indefinite, wherein "providing up to 8 combinations" = 1. The identity of one or more reference objects required for ascertaining "differential isotope labeled" is not clear, wherein "providing up to 8 combinations" = 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4-14, 17-23 and 32-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold *et al.* (US 6,670,194). With respect to independent claim 36:

Aebersold *et al.* describe a method for analysis of up to 8 samples (see col. 13, line 47, "more than two samples") of cellular extracts (see *e.g.*, col. 5, line 63, "cell or tissue lysates"; *see also*, col. 25, line 62, "cell lysate"), wherein the molecules have an amine bearing an active hydrogen (see col. 10, lines 30-41, "PRGs... include... those that react with amino groups"), the method comprising:

(i)(ii) providing and adding amine-containing sample to acetaldehyde and reducing agent (see *e.g.*, col. 13, lines 47-49, "sets of identical tagged peptides in which each set member is differentially isotopically labeled"; *see also*, col. 10, line 30, "protein reactive group"; *see also,* lines 51-52, "aldehydes or ketones in the presence... of $NaBH_4$ or $NaCNBH_3$" (paraphrasing mine); *see also*, col. 25, lines 48-49, "B-N(CD_3)[line break]CD_2CO— conjugate") (paraphrasing mine), thereby producing an isotopically-labeled alkylamine derivative.

(iii) combining derivatives (see col. 6, lines 2-3, "The treated samples are then combined");

(iv) separating derivatives into fractions (see col. 36, lines 11-12, "separated by 1D or 2D gel electrophoresis");

(v) enzymatically cleaving derivatives (see col. 19, lines 41-43, "proteolysis");

(vi) separating fragments (see col. 19, lines 41-43, "isolated by affinity chromatography");

(vii) examining derivatives by mass spectrometry (see Abstract, "reaction products are characterized by mass spectrometric (MS) techniques"); and

(viii) sequencing fragments (see col. 36, lines 19-36, "CID spectrum of a peptide contains sufficient information to identify the protein by searching sequence databases").

Claims 4-14, 17-23 and 32-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Vandekerckhove & Gevaert (US 6,908,740; formerly US 2004/0005633). With respect to independent claim 36:

Vandekerckhove & Gevaert describe a method for analysis of up to 8 samples (see col. 21, line 60, "two or more samples") of cellular extracts (see col. 7, line 31, "prokaryotic or eukaryotic cell lysate"), wherein the molecules have an amine bearing an active hydrogen (see col. 24, line 37-62, "α—NH_2-group, or ε—NH_2 groups of lysines"), the method comprising:

(i)(ii) providing and adding amine-containing sample to acetaldehyde and reducing agent (see *e.g.*, col. 24, lines 37-62, "labeling procedures based on known chemical reactions", "Schiff's-base formation with deuterated acetaldehyde followed by reduction with normal or deuterated

sodiumborohydride", "formaldehyde"), thereby producing an isotopically-labeled alkylamine derivative.

(iii) combining derivatives (see col. 22, line 4, "(c) combining");

(iv) separating derivatives into fractions (see col. 22, lines 6-7, "(d) separating the protein peptide mixture into fractions");

(v) enzymatically cleaving derivatives (see col. 22, lines 7-10, "(e) chemically, or enzymatically, or chemically and enzymatically altering at least one amino acid"; *see also*, col. 42, lines 52-53, "enzymatic cleavage");

(vi) separating fragments (see col. 22, lines 10-11, "(f) isolating the flagged peptides");

(vii) examining derivatives by mass spectrometry (see col. 22, lines 13-14, "(g) performing mass spectrometric analysis"); and

(viii) sequencing fragments (see col. 22, lines 17-18, "(i) determining the identity of the flagged peptide").

Response to Arguments

Prior Art Claim Rejections

In prior Office Action, claims 4-15, 17-23 and 32-36 were rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold *et al.* (US 6,670,194). Claim 16 was rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold *et al.* (US 6,670,194) in view of Vandekerckhove & Gevaert (US 2004/0005633).

In response, Applicants amend independent claims 32, 33 and 36 to add labeling reagents containing aldehyde AND reducing agent.

Applicants' amendment is not sufficient to overcome these rejections.

Upon more careful review, Aebersold *et al.* describe at col. 25, lines 48-49 the following "conjugate" (paraphrasing mine):

"B-N(CD_3)[line break]CD_2CO— conjugate"

The "conjugate" appears to consist of cyanoborohydride (*i.e.*, ""B-N(CD_3)") and acetaldehyde (*i.e.*, "CD_2CO").

Vandekerckhove & Gevaert describe what appears to be "labeling procedures based on known chemical reactions", including "Schiff's-base formation with deuterated acetaldehyde followed by reduction with normal or deuterated sodiumborohydride" (see *e.g.*, col. 24, lines 37-62).

Claim Rejections - 35 USC § 112 – second paragraph

In prior Office Action, claims 4-23 and 32-36 were rejected under 35 U.S.C. 112, second paragraph, because the phrase "differential isotope labeled reagents" was considered indefinite. Specifically, the number of chemically/isotopically distinct reagents was not clear.

In response, Applicants amend independent claims 32, 33 and 36 to add labeling reagents containing aldehyde AND reducing agent.

Applicants' amendment, supporting disclosure in the specification, and related argumentation is sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

Conclusion

No claims are allowable at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

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